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EXAMINER	
SINGH, SATYENDRA K	
ART UNIT	PAPER NUMBER
1657	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/572,811	EDENS ET AL.	
	Examiner	Art Unit	
	SATYENDRA K. SINGH	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-12,14,18-20 and 23-31* is/are pending in the application.

4a) Of the above claim(s) *8,14 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-12 and 23-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response (and amendments to claims and specification) filed on 11/12/2009 is duly acknowledged and entered.

Claims 8-12, 14, 18-20 and newly added claims 23-31 are currently pending in this application.

Claims 1-7, 13, 15-17, 21-22 have been canceled by applicants.

Claims 8, 14 and 18-20 have been withdrawn from consideration.

Election/Restrictions

Applicant's argument that the withdrawn claims 8, 14 and 20, and claims 18-19 share the same special technical feature as the elected invention of group V (see remarks, page 6, 2nd paragraph, in particular), is not found to be persuasive because as outlined in the restriction/election requirement (paper dated 11/24/2008), the "proline-specific endopeptidase" which is used in all the methods of making and using said endopeptidase has been disclosed in the prior art (EDENS et al, WO 02/45523, IDS), and therefore different inventions as claimed, lack unity. The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 8, 14 and 18-20 remain withdrawn from consideration.

Claims 9-12 and newly added claims 23-31 (invention of group V, elected specie "**celiac disease**") have been examined on their merits in this office action.

NOTE: Claims have been interpreted as generally directed to **a method of treatment** of patients in need thereof or patients suffering from "celiac disease", wherein the method requires oral (ingestion route) administration of a dietary supplement comprising a proline specific endoprotease having characteristics as recited in instant claims.

The following contains new grounds of rejection necessitated by applicant's current amendments to pending claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names **joint inventors**. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 9-12 and 23-31 (as currently presented) are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Messer et al (1976; IDS, citation UR) in view of Hausch et al (2002; [U]) and Dekker et al (WO 02/45524 A2; [N]).

Claims have been interpreted as generally directed to **a method of treatment of patients in need thereof or patients suffering from celiac disease** (elected specie), wherein the method requires oral (ingestion route) administration of a dietary supplement or a medicament (taken as a pharmaceutical composition) comprising a proline specific endoprotease (obtained from *Aspergillus niger*.; that can hydrolyze proline-rich peptides that are associated with celiac disease at a pH of below 5.5, or that has a pH optimum below 6.5; see specific recitations of claims 9-12 and new claims 23-31).

Messer et al (IDS) disclose a method of treatment of patients in need thereof or patients suffering from celiac disease, wherein the patients are orally administered a dietary formulation or supplement comprising a digestive enzyme (i.e. oral enzyme therapy to treat celiac disease; see entire report at page 1022) such as papain (in the form of enteric-coated tablets of commercially available papain) in order to help destroy the gluten to improve response to gluten free diet in the patients suffering from celiac disease, wherein based on their experimental results, they recommend oral, crude papain enzyme administration as an adjunct treatment to gluten-free diet in the treatment of gluten intolerance in patients in need thereof.

However, Messer et al do not use "**proline specific endoprotease**" that has the hydrolytic activity at **pH below 5.5, or a pH optimum of below 6.5** as required by the instant claims.

Hausch et al [U] disclose the immunodominant gliadin peptides that are now known to be the cause of celiac disease or gluten intolerance, and they show that these peptides are exceptionally resistant to enzymatic digestion in patients with such disorders as celiac disease (see abstract, and introduction, in particular). They also disclose the fact, that a trace amounts of exogenously added (both, *in vitro* or *ex vivo*) prolyl endopeptidase (albeit from a bacterial source) was able to efficiently destroy or digest said immunodominant peptides, suggesting "a possible enzyme therapy strategy for celiac sprue..." (see abstract, page G996, in particular). Hausch et al also state that "*...therefore, we suggest that supplementation of the celiac diet with bioavailable PEP, with or without DPP IV and DCP I, by virtue of facilitating gliadin peptide cleavage to nontoxic and/or digestible fragments may be useful in attenuating or perhaps even eliminating the inflammatory response to gluten. Such a strategy would be analogous to the*

enzyme therapy treatment in the case of lactose intolerance, where orally administered lactase is effective in cleaving and thereby detoxifying the lactose in milk product" (see page G1002, left column, and references contained therein)

Therefore, given the detailed disclosure by the cited prior art references of record, at the time this invention was made, it would have been obvious to a person of ordinary skill in the art to modify the method of treatment disclosed by Messer et al such that it uses a dietary supplement comprising prolyl endopeptidase as explicitly suggested and motivated by the disclosure of Hausch et al. Since, Hausch et al clearly demonstrated the use of prolyl endopeptidase in destroying the immunogenic gluten peptides that are known to be the root cause of the inflammatory response in patients with celiac disease, an artisan of ordinary skill in the art would be motivated to substitute the enzyme, papain with the prolyl endopeptidase of Hausch et al in order to successfully destroy the gliadin peptides, and thus achieve a superior and effective method of treatment of patients in need thereof.

However, the combined teachings of Messer et al and Hausch et al do not explicitly disclose the use of a prolyl endoprotease that has the hydrolytic activity at **pH below 5.5, or a pH optimum of below 6.5**, and that is obtained from an ***Aspergillus niger* sp.**

Dekker et al [N] disclose such an enzyme (a prolyl endoprotease that can hydrolyze proline-rich peptides that are associated with celiac disease at a pH of below 5.5, or that has a pH optimum below 6.5; i.e. mimicking stomach pH, and that has been derived from *Aspergillus* sp., specifically *Aspergillus niger*) that can be used for digesting or hydrolyzing various types of proteins and peptides to obtain hydrolysates that can be used in various applications, including allergen free diets for babies, and for obtaining wheat gluten hydrolysates which are normally

difficult to obtain (see Dekker et al, pages 3, 8 and 11, in particular; and claims) as it is poorly soluble at acidic pH. They disclose the extensive usefulness and application of this enzyme that acts in acidic conditions with a pH optimum below 6.5 (preferably pH 3.5 to 6.5), and that can be used to digest wheat gluten from barley into digestible peptides in order to protect gastric mucosa, which is normally at acidic pH.

Thus, given the disclosure from Dekker et al for a suitable prolyl endoprotease (derived from *Aspergillus* sp.) that can work best under the acidic pH conditions (such as of stomach and/or intestine of patients), an artisan of ordinary skill in the art would have been motivated to substitute a better prolyl endoprotease enzyme, albeit from an *Aspergillus* sp. such as *Aspergillus niger*, as explicitly taught by the referenced invention of Dekker et al in order to achieve a superior method (using an improved enzyme, that has an acidic pH optima, similar to the stomach environment) of treatment of patients suffering from celiac disease with a reasonable expectation of success, as evidenced by the detailed disclosure of Dekker et al that demonstrate the efficient digestion of various types of proteins using said prolyl endoprotease, albeit *in vitro*, having an acidic pH optimum, which will be suitable for the enzyme therapy (in the method of Messer et al and Hausch et al) as an oral dietary supplement for hydrolyzing potentially harmful peptides in the stomach, before they reach the intestine of sensitive patients.

Thus, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the art, at the time the claimed invention was made.

As per MPEP 2144.06, *In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. In re Ruff, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).*

As per MPEP 2111.01, *during examination, the claims must be interpreted as broadly as their terms reasonably allow. In re American Academy of Science Tech Center, F.3d, 2004 WL 1067528 (Fed. Cir. May 13, 2004)(The USPTO uses a different standard for construing claims than that used by district courts; during examination the USPTO must give claims their broadest reasonable interpretation.). This means that the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the specification. In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

Response to Applicant's Arguments

Applicant's arguments filed 11/12/2009 (as they pertain to the cited prior art of record) have been fully considered but they are not persuasive for the following reasons of record:

First, applicants seem to be arguing the cited references individually (see remarks, pages 7-9, in particular). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combined teachings of the cited prior art references as relied upon in the obviousness rejection of record provide a clear motivation to an artisan of ordinary skill in the art, and using a prolyl specific endopeptidase that can cleave the gluten peptides (from various sources such as wheat, barley, etc. that cause adverse reaction in celiac patients) at low or acidic pH (such as less than 6.5, as disclosed by the cited reference of Dekker et al) would have been an obvious improvement for the method of treatment as disclosed by Messer et al in view of Hausch et al.

Second, applicants seem to present the activity of proline specific endopeptidase at low or acidic pH and its use for digesting "proline-rich" peptides (includes gluten) as an unexpected result over the combined teachings of the prior art (see remarks, pages 8 and 10, in particular), especially as a oral supplement or medicament for patients having celiac disease, which is not

found to be persuasive because Dekker et al explicitly disclose such an enzyme (a prolyl specific endoprotease that can hydrolyze proline-rich peptides that are known to be associated with celiac disease, at a pH of below 5.5, or that has a pH optimum below 6.5, and that has been derived from *Aspergillus niger*) that can be used for digesting or hydrolyzing various types of proteins and peptides to obtain hydrolysates. This endopeptidase can be used in various applications, including allergen free diets for babies, and for obtaining wheat gluten hydrolysates which are normally difficult to obtain (see Dekker et al, pages 3, 8 and 11, in particular) as it is poorly soluble at acidic pH. They also disclose the extensive usefulness and application of said enzyme that acts in acidic conditions with a pH optimum below 6.5 (preferably pH 3.5 to 6.5), and that can be used to digest wheat gluten from barley into digestible peptides in order to protect gastric mucosa, which is normally at acidic pH.

Applicant's arguement that "(T)he prior art fails to teach or suggest this advantage of Applicants' administering proline specific endoprotease for ingestion by the patient such that the protease is active under the acidic conditions of the patient's stomach. Thus, the difference in locations (stomach vs. intestine) provides an unexpected result obtained by practicing Applicants' claimed invention" (see remarks, page 10, in particular), is fully considered but is not found to be persuasive because both Hausch et al and Dekker et al provide disclosure for the use of exogenous prolyl specific endopeptidase for pre-digesting immunodominant gluten or gliadin peptides (that is known to cause inflammation when they reach intestinal tissue of sensitive patients) present in food or for use as enzyme supplement therapy in order to eliminate harmful peptides before they reach the intestinal tissue after oral ingestion. Hausch et al (see p1002, left column, 3rd paragraph, in particular) specifically disclose such enzyme supplimentation therapy

to be "*analogous to the enzyme therapy treatment in the case of lactose intolerance, where orally administered lactase is effective in cleaving and thereby detoxifying the lactose in milk products*". In addition, Dekker et al discloses predigestion of various types of food proteins in order to make them less allergenic and suitable for consumption by populations in need thereof (see Dekker et al, page 7, last paragraph, in particular), including predigesting gluten peptides "*that contains prolamines with proline-rich peptide sequences*".

Thus, given the detailed disclosure in the cited prior art, an artisan of ordinary skill in the art, at the time this invention was made, would have fully contemplated the use of such an improved enzyme (for use as an oral supplement and/or medicament for oral administration) for the purposes of removing proline-rich immunogenic peptides from food compositions (either before they are ingested by celiac patients or populations in need thereof, or to be supplemented as a medicament wherein it helps digest the harmful peptides in the acidic environment of stomach owing to its pH optimum, before they reach the intestinal tissue) with a reasonable expectation of success. This is also evidenced by the disclosure of Dekker et al, which demonstrates *in vitro* predigestion of such allergenic peptides that are resistant to other commonly used proteases (for preparing protein hydrolysates for use in food compositions, for example) that are known in the art to cause inflammatory disorders of the intestine. Thus, the invention as currently claimed would have been fully contemplated and obvious to a person of ordinary skill in the art at the time the claimed invention was made. The 103(a) rejection is therefore properly made and maintained.

Conclusion

NO claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SATYENDRA K. SINGH whose telephone number is (571)272-8790. The examiner can normally be reached on 9-5MF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JON P. WEBER can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Satyendra K. Singh/
Examiner, Art Unit 1657

/JON P WEBER/
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